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Vector-based Vaccine/Cytokine Combination Therapy to Enhance Induction of Immune Responses to a Self-Antigen and Antitumor Activity.

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Many antigens associated with human tumors are overexpressed in tumor cells as compared with normal tissues; these "self" tumor-associated antigens are also expressed during fetal development, and it is, thus, not surprising that they are either weakly immunogenic or functionally nonimmunogenic in the tumor-bearing host. In the studies reported here, we have used different vaccines and vaccine strategies in an attempt to develop antitumor immunity in a stringent animal model. The tumor antigen used was human carcinoembryonic antigen (CEA). The model used was CEA transgenic mice, in which the human CEA transgene is under the control of the endogenous CEA promoter; CEA is expressed in fetal tissues and normal gastrointestinal tissues, and CEA protein is found in sera. Previous studies have shown these CEA transgenic mice to be tolerant to the induction of CEA immunity using CEA protein in adjuvant as an immunogen. CEA-expressing tumor cells were implanted 14 days before vaccine therapy. The vaccines used were recombinant vaccinia virus containing the transgenes for CEA and three T-cell costimulatory molecules [B7-1, ICAM-1, and LFA-3, designated recombinant vaccinia (rV)-CEA/TRICOM], with each transgene under the control of individual poxvirus promoters, and a replication-defective avipox virus (fowlpox; rF) containing the same four transgenes (designated rF-CEA/TRICOM). The results demonstrate that (a) continued boosting with vaccine is required to maintain CEA-specific T-cell responses, and boosting with rF-CEA/TRICOM is superior to boosting with rF-CEA; (b) a diversified vaccination protocol consisting of primary vaccination with rV-CEA/TRICOM followed by boosting with rF-CEA/TRICOM is more efficacious than homogeneous vaccination with rF-CEA/TRICOM in the induction of both CEA-specific T-cell responses and antitumor activity; and (c) the use of cytokines, local granulocyte macrophage colony-stimulating factor (GM-CSF) and low-dose systemic interleukin 2, in combination with vaccine is essential in inducing antitumor activity, as compared with the use of cytokines alone, or the use of vaccines without cytokine. Both GM-CSF and interleukin 2 were shown to contribute to the induction of CEA-specific T-cell responses. These studies thus provide a "proof of concept" that potent vaccines and vaccine strategies, in combination with cytokines, may be essential to obtain the level of T-cell responses directed against a self-antigen that is necessary to achieve antitumor responses.